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NANOINFORMATICS, COMPUTER APPLICATIONS FOR NANOMEDICINE

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Abstract: Nanoinformatics emerged in the early 21st century as a response to the need for computer applications at the nano level. While nanomaterials offer the potential for developing new devices in various industrial and scientific fields, they also provide revolutionary perspectives in disease prevention, diagnosis, and treatment in humans. This review paper analyzes different aspects of nanoinformatics with a special focus on nanomedicine. Another important aspect is the use of informatics in further advancing the biological and clinical applications of basic research in nanoscience and nanotechnology. Nanoinformatics can accelerate the development of the emerging field of nanomedicine, similar to what happened with the Human Genome and other -omics projects, through the exchange of modeling and simulation methods and tools, linking toxicity information with clinical and personal databases, or developing new approaches for scientific studies.

Keywords: Nanoinformatics, nanomedicine, nanocarriers, nanodrug, fullerenol.

Introduction

Over the past five decades, numerous computational methods and applications have been developed in the context of biomedicine, leading to interdisciplinary fields such as medical informatics, bioinformatics, and other related areas (Kulikowski, 2002). New informatics disciplines related to biomedicine encompass a wide range of scientific and technological approaches for addressing complex problems, including, among others, data and knowledge integration methods, biomedical ontologies and vocabularies, data and text mining, DNA and RNA sequencing, decision support in medicine, prediction of gene mutations and disease associations, development of data representation and exchange standards, as well as the development of informatics methods and tools for integrating multiple levels of data and creating simulations of biomedical systems. Mathematical and technical knowledge have successfully contributed to these research areas, leading to the complete realization of major global projects such as the Human Genome Project, computerization of clinical practice, or the creation of computer systems for decision suppor (Maojo, & Kulikowski, 2003). Numerous pioneering studies have been conducted, and after several decades, new scientific fields in nanomedicine have been discovered, holding promise for scientific and technological breakthroughs that can transform conventional medicine (Kim, Rutka, & Chan, 2010). Research in this field is often associated with nanotechnology, and there are many areas where computational methods themselves are crucial for advancing research and providing practical support (Maojo et al., 2010). These areas can be divided into fundamental groups.

Characterization of nanoparticles
Modeling and simulation
Imaging techniques
Terminologies, ontologies, and standards
Data integration and exchange
System interoperability
Data and text mining for nanomedicine research
Linking nano-information with computerized medical records
Basic and translational research
Networks of international researchers, projects, and laboratories
Education in nanoinformatics
Ethical considerations

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Nanoinformatics primarily deals with these issues, with the support of major organizations such as the U.S. National Science Foundation, the National Cancer Institute, and the European Commission. In this new context, nanoinformatics employs information techniques for the analysis and processing of information regarding the structure, physicochemical characteristics of nanoparticles and nanomaterials, their interaction with the environment, and their applications in nanomedicine (Maojo et al., 2011). These new applications emerge at a time when genomics and personalized medicine are gaining recognition and promising additional perspectives for biomedicine. The term "nanoinformatics" or "biomedical nanoinformatics" or "nanomedical informatics" can also be associated with other nanotechnology applications, but this work will only focus on the biomedical applications of nanodrugs in clinical oncology. According to the opinions of many scientists, nanomedicine is considered a new branch of medicine operating at a different, nano level, which entails significant physical and chemical differences. This poses great challenges for research, medical practice, and economic implications due to the novel toxicotherapeutic relationships at the nanoscale (Thomas, Pappu, & Baker, 2011). In that sense, we can recall what happened around 1995-2001 when bioinformatics contributed to the rapid completion of the Human Genome Project, and we can assume that informatics will also be crucial for progress in the development of nanomedicine. Nanomedicine encompasses a wide range of significant topics with practical and scientific implications, such as early disease detection, including cancer, the ability to achieve highly specific targeted therapies, new molecular imaging methods based on the optical properties of nanoparticles, drug delivery control methods in very small doses, nanorobots for diagnosis and therapy, hyperthermia treatments, and new approaches to overcoming solubility limitations of new or existing drugs (Kim, Rutka, & Chan, 2010; Thomas, 2023; Thapa, & Kim, 2023). In addition to human applications, nanoinformatics is also being developed in various branches of agriculture (Thakur, Kumari, & Dev, 2021; Borišev et al., 2016; Kojić et al., 2020). Researchers at the Polytechnic University of Madrid have developed a computer application based on text mining techniques, called "nanotoxicity searcher," which automatically searches for toxic information in scientific literature. In the searches conducted for paclitaxel, information on nanotoxicity was found, combined with appropriate ontologies such as the nanoparticle ontology (Thomas, Pappu, & Baker, 2011). This research and other efforts (de la Iglesia et al., 2011) have raised questions related to the management of information about nanotechnology, particularly:

1. The lack of appropriate standard classifications for nanomaterials.
2. The rapid development of knowledge about numerous complex biological, chemical, and physical processes occurring at the nanoscale.
3. The heterogeneity of information and structure in many scientific papers across various disciplines and sub-disciplines of nanotechnology.

All these issues increase the challenges of applying standard information retrieval methods in the literature without additional knowledge of the specificities within the presented scientific fields and subfields. New computer-based approaches are needed to effectively and efficiently connect information from nanomedicine, while considering the different levels of complexity encompassed in research, development, and application in nanotechnology. In this context, researchers proposed a direction for this field in the first decade of the 21st century (National Science Foundation, 2010).

Perspective for the applications of nanoinformatics

The contemporary approach to information retrieval involves comparing nanoinformatics with computational applications in biomedicine from six different perspectives."The Workshop on Nanoinformatics Strategies" was the first of its kind, held in Virginia in 2007 (Workshop on Nanoinformatics Strategies, 2007), followed by various professional conferences in the field. This workshop focused on practical engineering perspectives, without incorporating the existing computational infrastructure. Given the rapid development of nanoinformatics and the fact that nanotechnology deals with issues beyond medical and biological domains, it is expected that the use of nanomaterials will have an impact on human health. From a fundamental standpoint of quantum physics, very characteristic quantum effects and phenomena associated with nanoparticle size occur at the nanoscale, which do not manifest in bulk materials. This knowledge raises many questions about the use of new models and tools for predicting interactions between nanoparticles and biomolecules, as well as comparing the results of these models with in vitro and in vivo experimental measurements. Structuring information in nanomedicine is crucial for research development. New concepts have been introduced into the vocabulary, such as "nanoparticles" (National Library of Medicine. National Institutes of Health). New taxonomies and ontologies have been

developed, such as the nanomedicine ontology (Gordon, Sagman, & Alliance, 2003) and ontologies for nanotechnology indexes, along with the adoption of applications like BiomedGT for mapping across different ontologies (Baker et al., 2009).

Tools supporting the selection of nanomaterials for medical diagnostics, therapy, or theranostics should be based on several key criteria for nanoparticles, including size, shape, charge, chemical composition, topology, pharmacokinetics, biological activities or toxicity, and others.

In the late twentieth century, numerous initiatives were launched, such as the National Centers for Biomedical Informatics (USA) and the Virtual Physiological Human (VPH) program (Europe) (Viceconti, Clapworthy, & Van Sint Jan, 2008), to support biomedical research. A large number of projects are focused on modeling and simulating various systems, organs, tissues, and cells, as well as their relevance to applications in clinical practice. In addition to fundamental research in fields such as chemistry, physics, molecular biology, biochemistry, histology, and physiology, some engineering disciplines play a significant role in signal and image processing, modeling, and simulations, which can easily be adapted to nanoinformatics projects.

Among the most important information expected from such simulations are characterizations and simulations of the behavior of nanoparticles in biological models, the formation of interactions with target molecules in living systems, or the development of new imaging techniques using quantum dots (Network for Computational Nanotechnology, National Science Foundation, 2009; CaNanoLab). Researchers at the University of Talca in Chile, in collaboration with members of the National Cancer Institute-Frederick's Center for Advanced Biomedical Computing, have developed a database of nanostructure called the Collaboratory for Structural Nanobiology (Collaboratory for Structural Nanobiology).

Education in nanomedicine and nanoinformatics introduces new content from various scientific disciplines, such as the fundamentals of quantum physics and chemistry, new imaging modalities, modeling, and other areas. Experts with knowledge and skills in the application of nanoinformatics will play an important role in facilitating communication between different medical fields in the near future. The first step is undoubtedly the establishment of nanoinformatics infrastructure and the collection, cataloging, annotation, organization, and archiving of available data. The development and expansion of databases, software tools, and nanoparticles, including their physical and chemical properties, 3D structures, toxicity, and biomedical applications, are crucial.

Semantic interoperability of heterogeneous information systems containing nano and other data will be a key issue in nanoinformatics (Munteanu, 2011). Adapting the structure of scientific papers for ease of search and classification of nanoparticles is essential for establishing new hierarchies/taxonomies based on physical, chemical, clinical, and toxicological characteristics (Gerstein, Seringhaus, & Fields, 2007). 3D representations and visualization of molecular structures (O'donoghue, et al., 2010) can be adapted for visualizing nanoparticles. Adding information to understand changes in genotype caused by interactions with nanomaterials could provide new foundations and explanations for phenotypic traits. Hypothetically, a "nanotype" could include a large catalog of nanoparticles and biological interactions.

Modern nanomedicine requires new insights beyond current information technology, which is typically focused on collecting, displaying, and connecting heterogeneous information. In this broad multidisciplinary field, several fundamental questions have been recognized that need to be addressed, and one of them is the nanoparticle database. Other issues include diagnostic and therapeutic methods based on new nanomaterials, new models of electronic health records for personalized therapies, databases on the toxic and secondary effects of nanoparticles, and more. As an example, the collection of information on the application of nanoparticles as carriers for the antineoplastic agent doxorubicin (DOX) can be considered. Doxorubicin is an anthracycline antibiotic approved for clinical use as early as 1972. A major problem with the clinical application of this drug is its numerous adverse effects, with cardiotoxicity being the main concern. Over decades of research on this still indispensable chemotherapy drug, various approaches have been developed to reduce cardiotoxicity. One of them is the chemical synthesis of newer derivatives of doxorubicin. Several derivatives of doxorubicin have been developed to improve its pharmacological efficacy or reduce adverse effects. Some of these derivatives include daunorubicin, epirubicin, and idarubicin. However, this approach has not yielded the desired results in clinical practice. Another approach involves the use of cardioprotective agents such as Dexrazoxane, vitamin C, phenolic natural products, organic chelators, and others. In modern clinical practice, a combination of doxorubicin with other antineoplastic agents has been applied for a long time. The approaches mentioned above to address the fundamental problem of high cardiotoxicity have yielded minimal progress. A new strategy in the application of this drug is the synthesis of novel doxorubicin nanoformulations. Table 1 presents different groups of nanoparticles as carriers for doxorubicin.

Table 1. Groups of nanoparticles as carriers for doxorubicin

Various nanocarriers of doxorubicin	References
Gold nanoparticles	26
Polymeric nanoparticles	27
pH-responsive nanocarriers	28
Lipid nanocarriers	29
Magnetic nanocarriers	30
Carbon-based nanocarriers Fullerenes Carbonnanotubes Graphens	31,32
Other nanocarriares	33

Water-soluble polyhydroxylated derivatives of C60 fullerene, such as C60(OH)24 fullereneol, are nanoparticulate molecules capable of self-assembly in biological media, forming stable polyanionic nanoparticles ranging in size from 5 to 90 nm with a charge ranging from -20 to -55 mV, depending on the conditions (Djordjevic et al., 2015; Vraneš et al., 2017). Fullerene-based nanoparticle (FNP) has shown low cytotoxicity in in vitro studies and low acute, subacute, and chronic toxicity in in vivo models using mice and rats (Dragojevic-Simic et al., 2011). FNP exhibits high antioxidant properties in both chemical and biological models (Mirkov et al., 2004; Bogdanović et al., 2004; Trajković et al., 2007; Bogdanović et al., 2008; Milic et al., 2009; Stankov et al., 2013 Vesna et al., 2016 Kojić et al., 2020). FNP also possesses chelating properties, which were the basis for its cardioprotective potential in DOX applications (Đorđević et al., 2009). Moreover, FNP, in the presence of DOX, forms stable nanoparticles that have demonstrated significant cytotoxic effects on various malignant cell lines (Jović et al., 2016; Seke et al., 2016) while causing considerably fewer negative effects on vital organs in in vivo models (Injac et al., 2009a; Injac et al., 2009b; Torres et al., 2010; Milic Djordjevic et al., 2006; Injac et al., 2008a; Injac et al., 2008b; Injac et al., 2008c Borović et al., 2014; Srdjenovic et al., 2010; Vapa et al., 2012; Jacevic et al., 2017; Petrovic et al.,2018).

Conclusion

Computer engineering and the speed of information flow are developing rapidly. We are witnessing that quantum computers will be the leading technology in the near future. Nanotechnology began to be understood only from the middle of the last century, and in the past few decades, many scientific fields and applications based on nanomaterials have been developed. One of these fields is nanomedicine, which is increasingly being applied in clinical practice. A large number of scientific publications, fundamental and clinical studies, patents, numerous presentations at scientific conferences, and other sources provide information in the field of nanomedicine. A major challenge for the scientific community is how to classify and process all this information. Software programs have been developed that can recognize keywords in the field and classify information for both fundamental and applied research in biomedicine and clinical studies. By developing databases in the nano field and related software for simulating the interactions of nanoparticles in living systems, among other things, research time will be shortened, new mechanisms of action will be recommended, and overall resources will be saved. This approach has introduced a new, complex strategy for biomedical applications.

Conflict of interests

We have no known conflictof interest to disclose

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